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Reduction of plasma triglycerides by diet in subjects with chronic renal failure

MARY L. SANFELIPPO, ROBERT S. SWENSON and GERALD M. REAVEN

Department of Medicine, Stanford University School of Medicine and Veterans Administration Hospital, Palo Alto, California

Reduction of plasma triglycerides by diet in subjects with chronic renal failure. The response of plasma triglyceride levels to changes in the composition of meal formula diets was studied in 12 subjects who had moderate to severe chronic renal failure. Fasting hypertriglyceridemia (> 150 mg/100 ml) was present in seven of 12 subjects. Fasting plasma triglyceride levels decreased in all subjects in response to a reduction in the proportion of carbohydrate (from 50 to 35% of total daily calories) and an increase in the polyunsaturated to saturated fat ratio (from 0.2 to 2.0) in an isocaloric diet. Fasting plasma cholesterol and postprandial triglyceride levels were unchanged. Both the triglyceride production rate and the insulin response were significantly lower on a diet lower in carbohydrate and higher in polyunsaturated fat. These data indicate that hypertriglyceridemia occurs in subjects with moderate to severe chronic renal failure, and that dietary modification promptly reduces triglyceride levels over an 11 day period. A long term study on a dietary program incorporating these changes is indicated to determine whether this effect is sustained.

Deminution des triglycérides plasmatiques chez les sujets en insuffisance rénale chronique. La réponse des triglycérides plasmatiques aux modifications de la composition des régimes alimentaires a été étudiée chez 12 sujets atteints d'insuffisance rénale chronique modérée ou sévère. Une hypertriglycéridémie à jeun (150 mg/100 ml) existait chez sept parmi les 12 sujets. Les concentrations plasmatiques des triglycérides à jeun ont diminué chez tous les sujets en réponse à la diminution de la proportion d'hydrates de carbone (de 50% à 35% du total des calories) et à l'augmentation du rapport des acides gras non saturés aux acides gras saturés (de 0.2 à 2.0) dans un régime iso-calorique. Le cholestérol plasmatique à jeun et les triglycérides post-prandiaux n'ont pas été modifiés. La production de tryglycérides et la réponse à l'insuline ont été significativement diminuees au cours du regime pauvre en hydrates de carbone. Ces résultats indiquent que l'hypertriglycéridémie survient ches des sujets atteints d'insuffisance rénale chronique modérée on sévère et que les modifications diététiques réduisent rapidement l'hypertriglycéridémie sur une période de 11 jours. Une étude de longue durée d'un programme diététique utilisant ces données est utile pour savoir si l'effet obtenu est durable.

Elevated levels of plasma triglycerides have been reported in both dialyzed and undialyzed nonnephrotic patients with end-stage renal failure [1–7]. However, very little information is available concerning the levels of triglycerides in patients during the often long period of progression to end-stage renal failure. Such information could be particularly important because during that period patients are often placed on diets relatively low in protein. As a consequence they tend to eat increased amounts of carbohydrates and fats. A moderate increase in carbohydrate intake has been shown to elevate plasma triglycerides in subjects with normal renal function [8], and may account for similar elevations in patients with chronic renal failure.

The development of hypertriglyceridemia in patients with chronic renal failure is particularly relevant in view of the evidence that myocardial infarction, refractory congestive heart failure and cerebrovascular accidents are more common in patients with end-stage renal failure than in normal or hypertensive populations [9–12]. Recognition that cardiovascular disease is the leading cause of death in patients on chronic hemodialysis has heightened concern for potentially reversible attendant risk factors [13, 14]. In this regard, recent awareness of hypertriglyceridemia as a possible independent risk factor for the development of atherosclerotic heart disease is of critical importance. Three kinds of evidence link hypertriglyceridemia to the development of atherosclerotic heart disease. Earlier studies simply indicated that hypertriglyceridemia was commonly found in patients with atherosclerotic heart disease [15]. More recently, a nine-year prospective study demonstrated that elevated fasting plasma triglycerides were a risk factor for atherosclerotic heart disease independent of plasma cholesterol [16]. Finally, these observations have been supported by the demonstrated association between hypertriglyceridemia and angiographically documented coronary artery disease [17]. At the same time, considerable evidence exists which argues that hypertriglyceridemia *per se* is not an independent risk factor for the development of atherosclerotic heart disease [18–20]. However, as Brunzell and co-workers have pointed out, the situa-

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tion might be very different when the hypertriglyceridemia exists in conjunction with other risk factors such as diabetes or renal failure [21], and in these situations it is certainly possible that hypertriglyceridemia accentuates the risk of developing atherosclerotic heart disease. If hypertriglyceridemia occurs early in the course of renal failure, early intervention may help avoid chronic elevations of plasma triglycerides, which could predispose patients to atherosclerosis. We undertook this study in an attempt to address both of these issues. Our approach has been to study patients prior to the development of end-stage renal failure to *a*) define the levels of triglycerides seen during moderate to severe chronic renal failure, and *b*) determine whether the triglyceride levels in these patients would respond to modification simply by dietary manipulation.

Methods

Patients. Twelve non-nephrotic subjects with chronic renal failure were selected from the outpatient renal clinics of Stanford University Medical Center and the Palo Alto Veterans Administration Hospital. None of the patients were on insulin, prednisone, androgenic steroids or lipid-lowering agents prior to study. All had documented creatinine clearance determinations of less than 50 ml/min and hematocrit values of 25% or greater at the initiation of the study. Selection criteria excluded patients with recent myocardial infarction or cerebrovascular accident, uncontrolled hypertension or serum albumin less than 3.0 g/100 ml. Selection was made without regard to a history of lipid abnormalities.

Protocol. Subjects were admitted to the Stanford General Clinical Research Center and assigned to one of two isocaloric formula (liquid) diets. [Formula diets were used to facilitate controlled metabolic studies. However, the contents are readily convertible into a practical meal-planning program. Essentially this involves manipulating the proportions of total daily calories supplied by carbohydrates and fats, the polyunsaturated to saturated fat ratio, and the cholesterol content. The proportion of total calories supplied as protein is maintained at 10%. (See Appendix.)] Both diets contained 35 calories/kg of body wt per day and were given as one-fifth of total calories at 8 AM, two-fifths at noon and two-fifths at 5 PM. Weights were stable throughout the study.

One diet, the "conventional" diet, was designed to simulate the diet most subjects were considered to be eating at home. It contained 10% of total calories as protein, 50% as carbohydrates and 40% as fat. Cholesterol content was 600 mg/day. Polyunsaturated to saturated fat ratio was 0.2. The second diet, a "low carbohydrate" diet, also contained 10% of total calories as protein. However, the carbohydrate content was reduced from 50 to 35%. To maintain caloric balance, fat content was increased from 40 to 55%, but the type of fat was changed to yield a polyunsaturated to saturated fat ratio of 2.0. In addition, the cholesterol content was reduced to 300 mg/day. Thus, the "low carbohydrate" diet was, in fact, low in both carbohydrate and cholesterol and relatively high in polyunsaturated fat. For the sake of brevity, it will hereafter be referred to as the "low carbohydrate" diet. Contents of sucrose, sodium, and potassium were identical in both diets.

A single blind cross-over design was used. That is, subject 1 began on the conventional diet. After the 11-day period, he switched to the "low carbohydrate" diet. Subject 2 began on the "low carbohydrate" diet, then switched to the conventional diet, and so on. After three days on the conventional diet, an oral glucose tolerance test was done [22]. The sequence of tests that occurred during each 11-day period was as follows: *1*) fasting glucose, insulin, triglyceride, cholesterol, free fatty acid, and growth hormone levels were obtained on days 4, 7, 10 and 11; *2*) a meal tolerance test was performed on day 7, during which plasma glucose, insulin and triglyceride levels were measured in response to the lunch meal. For this purpose, a blood sample was taken just prior to ingestion of the noon meal, and again at 1, 2 and 3 PM; *3*) determination of triglyceride turnover rate was performed on day 11. An injection of 300μCi of tritium-labeled glycerol was given intravenously at 8 AM. Subjects received one-twelfth of the day's formula at 2 PM and 5 PM to maintain constant plasma triglyceride levels. Blood samples were drawn at 10 AM, 11 AM, noon, 2, 5 and 8 PM for measurement of the resultant triglyceride specific activity. The triglyceride turnover rate was then calculated from the triglyceride specific activity time-curve by a previously described technique [23]. Since these studies were carried out under steady state conditions, turnover rate = removal rate = production rate. Therefore, hereafter triglyceride turnover rate will be referred to as triglyceride production rate.

Analytical Methods. Blood for glucose, triglycerides and cholesterol determinations was withdrawn into tubes containing disodium EDTA; blood for free fatty acids was withdrawn into tubes with sodium heparin. Blood specimens were separated immediately by ultracentrifugation and all samples stored at 4°C. Plasma glucose concentrations were measured by an oxygen rate modification of the glucose oxidase method adapted for the Beckman Glucose Analyzer [24]. Immunoreactive insulin and growth hormone

levels were measured by a modification of the method of Desbuquois and Aurbach [25]. Plasma triglyceride and cholesterol levels were determined with an autoanalyzer (Technicon, methods N-78 and N-24a, respectively). Free fatty acids were measured by the method of Antonis [26]. Ideal weights were determined according to the 1960 Metropolitan Life Tables.

Statistical methods employed included Spearman's rank correlation coefficient and Pearson's product-moment correlation coefficient, a cross-over design analysis of ratios for comparison of responses on the two diets and of areas under the insulin response curves, and an analysis of variance F test.

Results

The study group was composed of ten males and two females with mean age (± standard error, SEM) of 42 ± 3 years (range, 25 to 60). The mean creatinine clearance determination, corrected for body surface area, was 19 ± 3 ml/min (range, 7 to 36). The mean body weight was 78.9 kg (range, 55.3 to 102.5). The mean relative weight for the group was 113%. Two subjects had relative weights above 120%, but both had fasting triglyceride levels well within one standard deviation of the mean. Three subjects had abnormal values for the glucose tolerance tests by the revised criteria of Fajans and Conn [22, 27].

Figure 1 depicts the effect of the two diets on fasting plasma levels of triglycerides, cholesterol, glucose, and insulin for the 12 subjects. Mean values were calculated from an average of 3 to 4 measurements for each subject. Mean (± SEM) fasting plasma triglyceride levels for the group on the conventional diet were 256 ± 57 mg/100 ml. Seven of the 12 subjects on the conventional diet had fasting values above 150 mg/100 ml. Six of 12 were over 200 mg/100 ml. Fasting triglyceride levels fell in each subject on the "low carbohydrate" diet to a mean of 169 ± 36 mg/100 ml. This difference was significant ($P < 0.001$). Fasting values for cholesterol, glucose and insulin were similar on the two diets. Free fatty acid and growth hormone levels, not shown, were also similar on the two diets. Thus, the "low carbohydrate" diet led to a fall in fasting triglyceride levels. The concomitant increase in fat did not lead to a rise in fasting cholesterol, presumably because of the increased polyunsaturated to saturated fat ratio and the decrease in dietary cholesterol. No correlation by either Spearman's or Pearson's coefficient was found between the following variables: *a*) either the creatinine clearance or the degree of azotemia and fasting triglyceride levels, *b*) fasting triglycerides and cholesterol levels, *c*) either age or relative weights and fasting triglyceride levels.

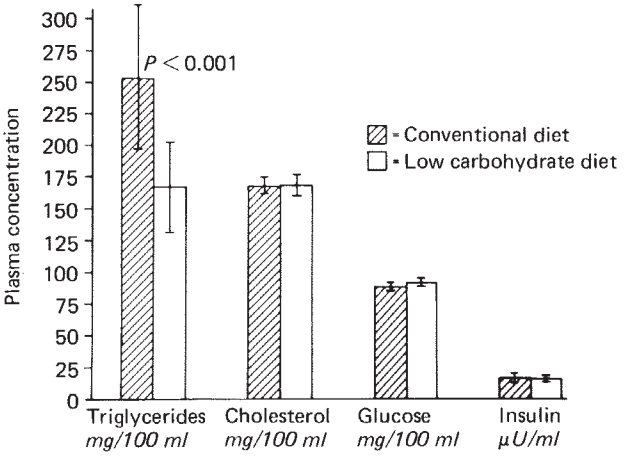

Fig. 1. *Effect of diet on fasting plasma levels of triglycerides, cholesterol, glucose and insulin (mean ± SEM).* Triglyceride levels were significantly lower on the "low carbohydrate" diet ($P < 0.001$).

Since the "low carbohydrate" diet contained 15% more fat than the conventional diet, it might be expected to increase postprandial fat levels, and, therefore, to diminish the benefits achieved by decreasing fasting triglyceride levels. However, no such elevation was observed, as illustrated in Figure 2. This graph shows the effect of the "low carbohydrate" diet on postprandial triglyceride levels. Fasting values for that day are also shown. Mean values for the group

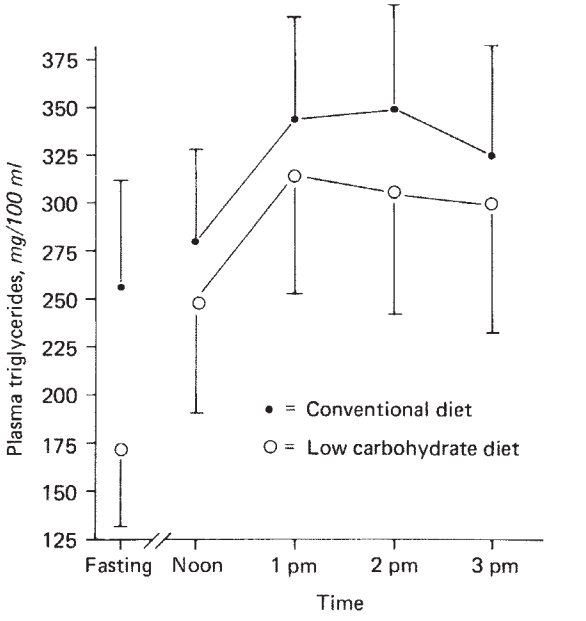

Fig. 2. *Effect of low carbohydrate diet on fasting and postprandial triglyceride levels (mean ± SEM for the group).* Fasting values for that day are also shown.

(± SEM) are shown before breakfast and at noon, 1, 2 and 3 PM. Noon values were obtained just prior to meal ingestion. Fasting triglyceride values that day were significantly lower on the "low carbohydrate" diet. Although postprandial triglyceride levels tended to increase more on the "low carbohydrate" diet, at no time did they exceed the triglyceride levels attained on the conventional diet. (All values for a given subject were determined during the same assay.) In fact, postprandial triglyceride levels remained lower at each time point on the "low carbohydrate" diet, but the differences were no longer significant.

Thus, by decreasing the carbohydrate intake, we achieved a fall in fasting triglycerides without a concomitant increase in cholesterol or postprandial triglyceride levels. In order to help elucidate the mechanism of the decrease in fasting plasma triglyceride levels, we determined triglyceride production rates on both diets. Results are plotted in Figure 3, along with a curve describing the relationship between plasma triglyceride concentration and production rate in subjects with normal renal function studied previously by Olefsky, Farquhar, and Reaven [23]. Several points can be made from these data. In the first place, plasma triglyceride levels directly correlated with triglyceride production rates ($r = 0.78$, $P < 0.001$). Second, the fall in triglyceride concentration that occurred in each patient was associated with a fall in triglyceride production rate ($P < 0.001$). However, the fact that the decreases in triglyceride level were associated with decreases in triglyceride production rate does not mean that the initial hypertriglyceridemia was due to greater than normal rates of triglyceride production in these subjects. Indeed, inspection of Figure 3 suggests the converse, i.e., most experimental points fall below the curve describing the relationship between plasma triglyceride level and production rate previously observed in normal individuals. In other words, patients with chronic renal failure had a higher triglyceride level than did normal subjects at any given triglyceride production rate. In order to analyze this relationship more thoroughly, we compared the observed ratio of plasma triglyceride concentration to turnover rate in our male patients (10 of 12 subjects) with the ratio observed in male patients previously described by Olefsky, Farquhar, and Reaven [23]. In nine of our ten male subjects, the observed ratio was higher than that previously observed ($P < 0.001$ analysis of variance F test), indicating that these patients remove very low-density lipoproteins (VLDL) from plasma less efficiently than do normal subjects.

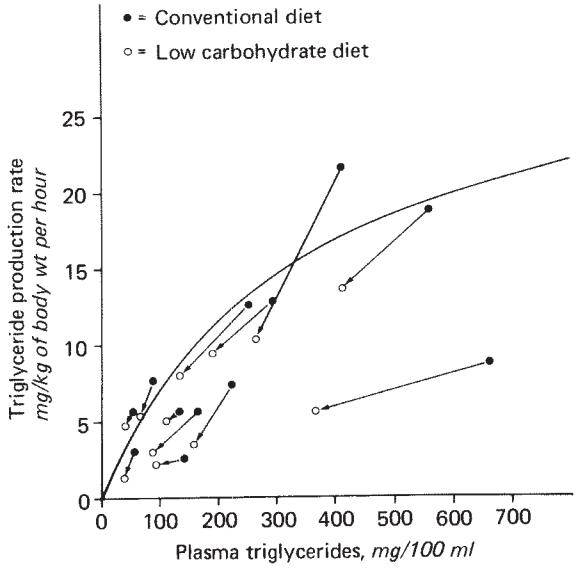

Fig. 3. *Relationship between triglyceride production rate and triglyceride concentration for subjects on each diet.* Hyperbolic *curve* portrays this relationship as seen in a group of normals previously studied in our center.

Previous studies in subjects with normal renal failure have demonstrated that the triglyceride response to a given diet is closely related to the evoked insulin response [28, 29]. To determine whether this was the case in our patient population, we examined the insulin response to meals in our subjects on both diets. Results seen in Figure 4 show that the insulin response (area under the curve) was less on the "low carbohydrate" diet in 11 of 12 subjects, and the mean insulin response was significantly lower ($P < 0.05$).

Discussion

The results of our studies indicate that hypertriglyceridemia can develop in patients with renal disease prior to the occurrence of end-stage renal failure. The mean fasting plasma triglyceride level in these subjects on the conventional diet was 256 mg/100 ml; seven of the 12 subjects had plasma triglyceride levels greater than 150 mg/100 ml, and six of the subjects had triglyceride levels greater than 200 mg/100 ml. These values are certainly greater than might be anticipated in a comparable population in the absence of renal disease [30], and suggest that a prolonged period of hypertriglyceridemia occurs in the natural history of patients with chronic renal disease. However, these results also indicate that a relatively moderate decrease in dietary carbohydrate intake (and associated increase in polyunsaturated fat) can lead to a significant fall in plasma triglyceride levels in all subjects. Furthermore, this effect was produced without a concomitant increase in either postprandial triglyceride or fasting cholesterol levels. In the former

case it appears that the degree of fall in fasting plasma triglyceride levels on the "low carbohydrate" diet more than compensated for the relatively greater increase in postprandial triglyceride levels, thus leading to triglyceride levels which were always lower than those on the conventional diet. Furthermore, the fall in postprandial plasma triglycerides continued over the period of observation. There is no reason to suspect that the levels would increase prior to ingestion of the dinner meal.

The lack of a rise in plasma cholesterol levels was most likely due to the fact that the cholesterol intake was decreased and the polyunsaturated to saturated fat ratio increased in the "low carbohydrate" diet. We feel that the 15% decrease in carbohydrate intake alone could account for the fall in plasma triglyceride levels, since previous studies of patients with normal renal function have shown that similar modifications of carbohydrate intake have had a comparable impact on plasma triglyceride levels [8]. On the other hand, this does not mean that the triglyceride-lowering effect of the diet was totally due to low carbohydrate, since others have shown that substituting polyunsaturated fat for saturated fat in the diet also lowered triglycerides (TG), and that this effect may be accomplished by increasing VLDL-TG removal rate [31, 32]. Thus, it is difficult to separate out effects of carbohydrate and fat. To conclusively demonstrate the role of carbohydrate alone in the production of hypertriglyceridemia would require a third dietary period involving 50% carbohydrate, 40% fat, 10% protein, 300 mg cholesterol and a polyunsaturated to saturated fat ratio of 2. However, our goal was not to define the discrete dietary variable responsible for hypertriglyceridemia in these subjects. Rather we have attempted to determine whether plasma triglyceride levels in these subjects would respond to relatively simple dietary modification.

The fall in fasting triglyceride level produced by the "low carbohydrate" diet was associated with a decrease in triglyceride production rate, possibly secondary to a decrease in the insulin response elicited by that diet. However, this does not necessarily imply that greater than normal production rates are the cause of hypertriglyceridemia in patients with chronic renal failure. In fact, the opposite generalization seems more likely. Thus, the data in Figure 3 indicate that the relationship between plasma triglyceride concentration and production in patients with renal failure differs somewhat from that described in subjects with normal renal function. In general, triglyceride levels appear to be higher than normal in patients with renal failure at a given triglyceride production rate, suggesting that a defect in VLDL removal is

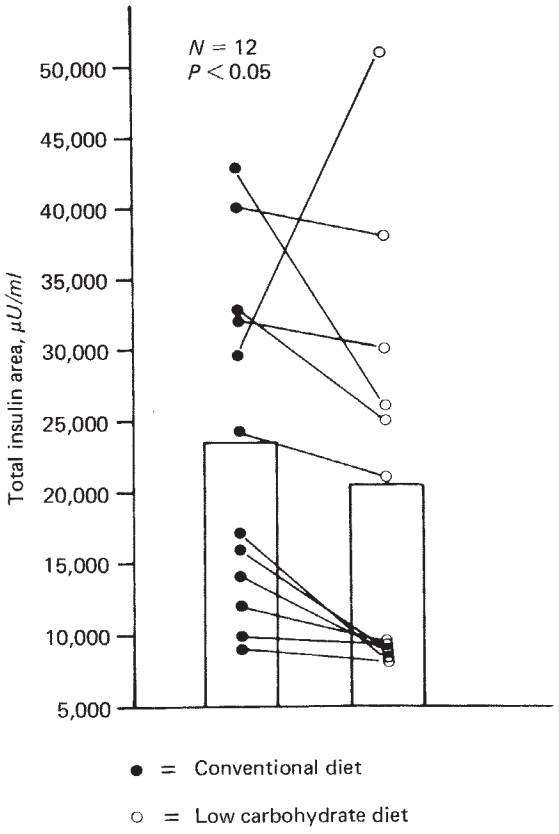

Fig. 4. *Insulin responses of individual subjects to noon meal.* Total insulin area expresses area *under the curve* calculation. *Bars* depict group mean on each diet.

responsible for the hypertriglyceridemia. Similar data have already been reported by Cattran and co-workers [7], who compared the relationship between plasma triglyceride levels and production rates observed in a group of patients with end-stage renal failure to the relationship between these two variables observed by Nikkilä and Kekki [33] on a group of normal subjects. They also noted that patients with chronic renal failure had a greater triglyceride level for any given triglyceride production rate than did the normal subjects, and they postulated that a defect in triglyceride removal was responsible for the development of hypertriglyceridemia. The notion that VLDL removal defect is present in patients with uremia is also supported by the work of several groups who have described a decrease in plasma postheparin lipolytic activity in uremic subjects [2, 34, 35]. On the other hand, it should be remembered that measurements of plasma postheparin lipolytic activity provide only an indirect measurement of VLDL removal rate. Furthermore, it must also be emphasized that neither we nor Cattran et al [7] studied large numbers of patients. In addition, we are both

comparing the relationship between triglyceride concentration and production rates in patients with renal failure to the relationship that existed between these two variables in normal subjects studied at some other time. Furthermore, a question has been raised as to the validity of comparing results of plasma triglyceride turnover data in subjects on different diets [36]. In this regard, previous work in our laboratory on several different diets demonstrates no systematic variation from the normal relationship between triglyceride concentration and turnover (or production) rate utilizing the currently employed technique [28, 37]. Finally, it is also clear from Figure 3 that heterogeneity exists in the relationship between triglyceride level and production rate in the patients we studied, and that this relationship appeared to be completely normal in some patients with renal failure. Thus, although we believe that the current data are most consistent with the hypothesis that a defect in VLDL removal is the major cause of hypertriglyceridemia in patients with chronic renal failure, we feel that final judgment should await the evaluation of triglyceride kinetics in a larger number of subjects.

On the other hand, even if a defect in VLDL removal will eventually prove to be the sole defect responsible for hypertriglyceridemia in patients with renal failure, it does not mean that efforts aimed at decreasing VLDL production rate will not be therapeutically useful. Thus, the data in Figure 3 clearly indicate that a significant direct correlation exists between triglyceride production rate and concentration in uremic subjects, e.g., the higher the production rate, the higher the concentration. This may be especially pertinent in view of the fact that plasma cholesterol levels, an established risk factor for atherosclerosis in nonuremic subjects, are generally normal or only modestly elevated in subjects with chronic renal failure. Since subjects with chronic renal failure have elevated levels of plasma triglycerides, and since hypertriglyceridemia may be a risk factor for atherosclerosis in subjects with normal renal function, hypertriglyceridemia may be partially responsible for the increased risk of developing atherosclerotic heart disease in these subjects. In fact, plasma triglycerides may play a greater role in these subjects than in those with normal kidney function [21]. For this reason it seems reasonable to attempt to lower triglyceride production rates, and consequently triglyceride levels, in these patients. Our results demonstrate that this can be accomplished by dietary modification. It is possible that manipulation of the polyunsaturated to saturated fat ratio alone would yield similar results to those achieved in this study. However, since high carbohydrate intake is known to cause hypertriglyceridemia, we recommend avoidance of a high carbohydrate intake in conjunction with lowered cholesterol intake and increased polyunsaturated fat. Another possible approach, the administration of lipid-lowering drugs, e.g., clofibrate, has been recently shown to be associated with serious complications [38, 39]. In view of these problems we would suggest that dietary modification, which does not on initial study appear to be associated with attendant risks, may offer an approach which is both safer and more physiologic. Obviously, further study is required to determine whether this approach can safely produce sustained reduction over a significant length of time. In addition, studies are now in progress to determine whether dietary modification will be equally effective in subjects already on chronic hemodialysis. A long-term follow-up study on nonformula meals with the recommended dietary prescription is also under consideration. The results of these investigations should lend further insight into the potential application of dietary changes to control of hypertriglyceridemia in patients with chronic renal failure.

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Appendix

A. Low carbohydrate, low cholesterol, high polyunsaturated fat diet

1. Proportion of constituents:
   35% carbohydrate
   10% protein
   55% fat, polyunsaturated to saturated fat ratio, 2.0
2. Amounts (gm) for 70 Kg reference man:
   214 gm of carbohydrate
   61 gm of protein
   150 gm of fat (includes 300 mg cholesterol)
   2450 calories

B. Sample menu:

Breakfast
1 cup dry cereal/1 tsp sugar
1/2 cup Mocha Mix[a]
1/2 cup nonfat milk
2 slices toast
4 tsp. margarine[b]
1/2 cup orange juice
coffee with 1 tsp. sugar and
1 oz. Mocha Mix

Lunch
2 slices bread
2 oz. meat[c]
1-1/2 tbsp. mayonnaise/margarine
green salad with 1-1/2 tbsp. dressing
coffee with 1 oz. Mocha Mix and
1 tsp. sugar

Dinner
3 oz. meat
1 cup rice
2 tbsp. margarine
green salad with 1 tbsp.
dressing
vegetables with 1 tsp. margarine
1/2 cup canned pears
coffee with 1 oz. Mocha Mix
and 1 tsp. sugar
1/2 cup nonfat milk

Snack
coffee with 1 oz. Mocha Mix
and 1 tsp. sugar

[a] Non-dairy creamer containing polyunsaturated fat
[b] Soft tub type using corn oil or safflower oil base
[c] Poultry, veal, fish; lean cuts of beef, lamb, ham, pork

Reprint requests to Dr. Mary L. Sanfelippo, Veterans Administration Hospital (111-R), 3801 Miranda Avenue, Palo Alto, California 94304, U.S.A.

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